The International Liver Congress™
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ENDURANCE-3: SAFETY AND EFFICACY OF GLECAPREVIR/PIBRENTASVIR COMPARED TO SOFOSBUVIR PLUS DACLATASVIR IN TREATMENT-NAÏVE HCV GENOTYPE 3-INFECTED PATIENTS WITHOUT CIRRHOSIS

Reported by Jules Levin
The International Liver Congress (EASL) - Amsterdam, The Netherlands 21 April 2017

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AASLD: SURVEYOR-II, PART 3: EFFICACY AND SAFETY OF GLECAPREVIR/PIBRENTASVIR (ABT-493/ABT-530) IN PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 3 INFECTION WITH PRIOR TREATMENT EXPERIENCE AND/OR CIRRHOSIS - (11/14/16)

EASL: 100% SVR12 WITH ABT-493 AND ABT-530 WITH OR WITHOUT RIBAVIRIN IN TREATMENT-NAÏVE HCV GENOTYPE 3-INFECTED PATIENTS WITH CIRRHOSIS - (04/19/16)

EASL: HIGH SVR RATES WITH ABT-493 + ABT-530 CO-ADMINISTERED FOR 8 WEEKS IN NON-CIRRHOTIC PATIENTS WITH HCV GENOTYPE 3 INFECTION - (04/18/16)

Summary: ENDURANCE-3

Glecaprevir/Pibrentasvir (300 mg/120 mg) was well-tolerated with a safety profile comparable to SOF + DCV

G/P achieved high efficacy in non-cirrhotic, treatment-naïve patients with chronic HCV GT3 infection

- 12 weeks of G/P was non-inferior to 12 weeks of SOF + DCV
- 8 weeks of G/P was non-inferior to 12 weeks of G/P
  - 95% SVR12 after 8 weeks of G/P

Additional G/P Posters Available at EASL

Integrated safety of G/P in patients with cirrhosis	THU-263 20 Apr, 8:00-18:00
Integrated resistance analysis in Phase 2 and 3 studies of G/P	FRI-205 21 Apr, 8:00-18:00
Integrated safety of G/P in patients without cirrhosis	FRI-238 21 Apr, 8:00-18:00
Integrated efficacy of 8 versus 12 weeks of G/P	SAT-233 22 Apr, 8:00-18:00
Integrated safety and efficacy of G/P by CKD stage	SAT-273 22 Apr, 8:00-18:00

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abbvie

HCV Genotype 3 and Treatment Options

Chronic hepatitis C virus (HCV) genotype (GT) 3 infection is common and progressive[1,2]

- Prevalent among people who inject drugs

In GT3, DAA therapies have shown lower rates of sustained virologic response (SVR)[3]

EASL-recommended treatments for treatment-naïve patients without cirrhosis are[4]:

- Sofosbuvir + daclatasvir (12 – 24 weeks)
- Sofosbuvir/velpatasvir (12 weeks)

Shorter treatment duration could enhance patient adherence and access to treatment[5]

1. Blach S, et al. *Lancet Gastroenterol Hepatol* 2016; 2:161-176.
2. Gower E, et al. *J Hepatol* 2014; 61:S45-57.
3. Ampuero J, et al. *Aliment Pharmacol Ther* 2014; 39:686-98.
4. European Association for the Study of the Liver. *J Hepatol* 2017; 66:153-194.
5. Younossi ZM, et al. *Aliment Pharmacol Ther* 2014; 39:518-31.

Next Generation Direct-Acting Antivirals (G/P): I

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Coformulated: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

Clinical pharmacokinetics and metabolism

- Once-daily oral dosing
- Minimal metabolism and negligible renal excretion (<1%)

G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta.

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Next Generation Direct-Acting Antivirals (G/P): II

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A
protease inhibitor

Coformulated: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A
inhibitor

***In vitro* characteristics**[1,2]

- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, 168) and NS5A polymorphisms (eg, positions 28, 30, 31, 93)
- Highly active against HCV GT3

G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta.

1. Ng TI, et al. *Antimicrobial Agents and Chemotherapy;* 2017 (in press). 2. Ng TI, et al. Abstract 636. CROI, 2014

Next Generation Direct-Acting Antivirals (G/P): III

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A
protease inhibitor

Coformulated: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A
inhibitor

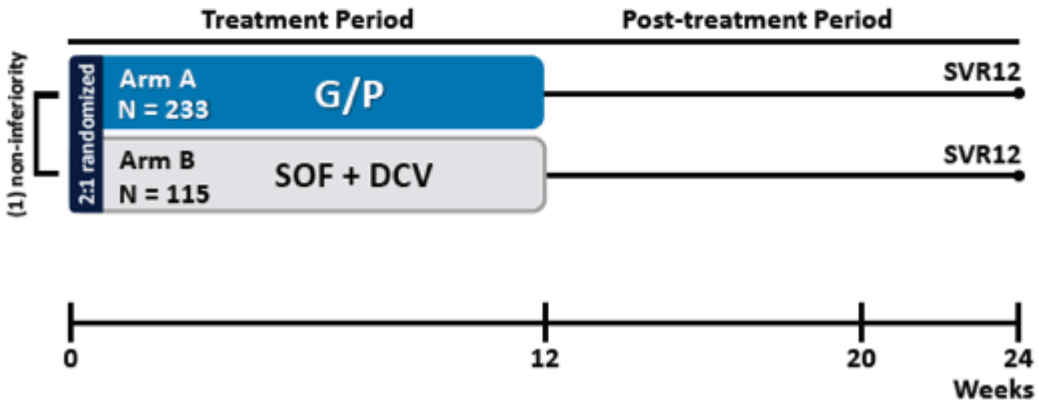
Prior phase 2 and 3 studies

- G/P for 8 weeks: 97% (28/29) SVR12 rate with no virologic failures in treatment-naïve GT3 patients without cirrhosis[1]
- SURVEYOR-II, Part 3: G/P for 12 weeks: 98% (39/40) SVR12 rate in GT3 patients with cirrhosis[2]

G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta

1. Muir AJ, et al. *The International Liver Congress (EASL).* 16 Apr 2016.
2. Wyles D, et al. *The Liver Meeting (AASLD).* 13 Nov 2016.

ENDURANCE-3: Objective and Study Design

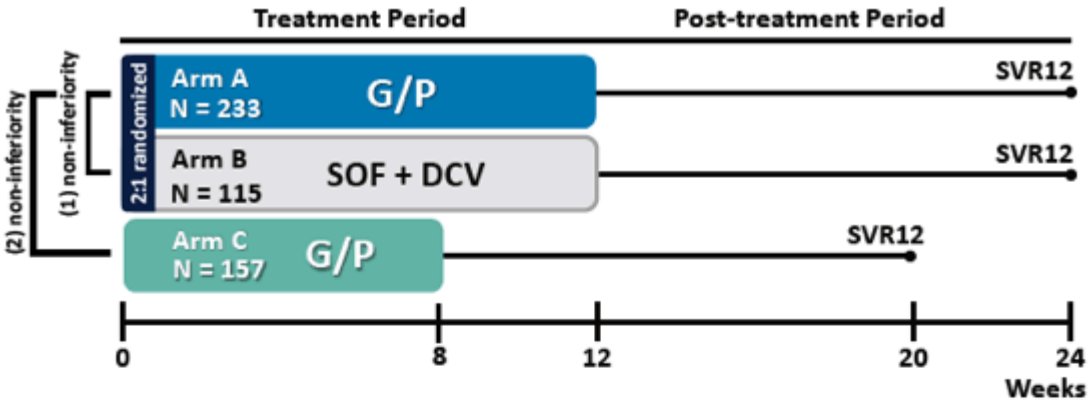


Objective

Determine the efficacy and safety of G/P in non-cirrhotic, treatment-naïve patients with HCV GT3

- SVR12: Non-inferiority of 12 weeks of G/P compared to 12 weeks of SOF + DCV

ENDURANCE-3: Objective and Study Design



Arm C: 8-week treatment duration

Per discussion with regulatory authorities after phase 2 treatment data became available, an 8 week treatment Arm of G/P was added to the study design

- SVR12: Non-inferiority of 8 weeks of G/P compared to 12 weeks of G/P*

*Endpoint was tested only after 12 weeks of G/P was determined non-inferior to 12 weeks of SOF + DCV

ENDURANCE-3 Patient Criteria

Key patient inclusion criteria

- ≥18 years of age (no upper limit)
- Chronic HCV GT3 infection (HCV RNA ≥1000 IU/mL)
- Absence of cirrhosis (METAVIR score ≤3, or equivalent)
- Treatment-naïve

Key patient exclusion criteria

- HBV or HIV coinfection, or infection with more than one HCV genotype
- Alanine or aspartate aminotransferase >10 × ULN
- Albumin < LLN

Positive toxicology tests in urine or active illicit or intravenous drug use were not exclusionary

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Baseline Demographics and Clinical Characteristics

Characteristic	2:1 randomized G/P 12 weeks N = 233	2:1 randomized SOF + DCV 12 weeks N = 115	Non-randomized G/P 8 weeks N = 157
Male, n (%)	121 (52)	52 (45)	92 (59)
White race, n (%)	205 (88)	103 (90)	134 (85)
Age, median years (range)	48 (22 – 71)	49 (20 – 70)	47 (20 – 76)
BMI, median kg/m^2 (range)	25 (17 – 49)	25 (18 – 42)	26 (18 – 44)
HCV RNA, median $\log_{10}$ IU/mL (range)	6.1 (3.5 – 7.5)	6.0 (3.8 – 7.4)	6.1 (1.2 – 7.6)
History of injection drug use, n (%)	149 (64)	73 (63)	104 (66)
Baseline fibrosis stage, n (%)			
F0 – F1	201 (86)	97 (84)	122 (78)
F2	12 (5)	8 (7)	8 (5)
F3	20 (9)	10 (9)	27 (17)
Subtype GT3a, n/N (%)*	226/229 (99)	113/113 (100)	154/155 (99)

BMI, body mass index; DCV, daclatasvir; G/P, coformulated glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; SOF, sofosbuvir
*HCV subtype determined by phylogenetic analysis; N = total number of patients with sequence data available

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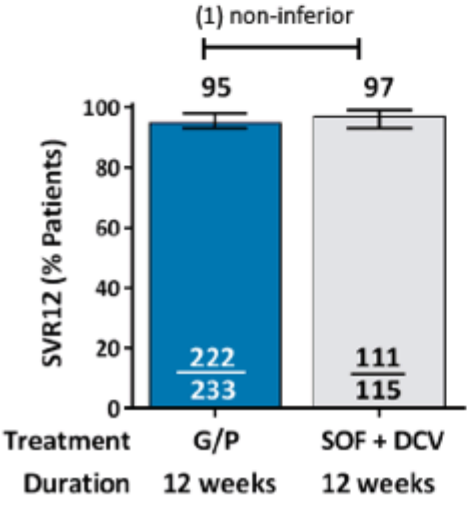
SVR12 by Intent-to-Treat (ITT) Analysis



Non-inferiority:
Lower bound of the confidence interval (CI) of the difference in SVR12 must be above -6%*

(1) -1.2% (95% CI -5.6 – 3.1)

*Conventional statistical methods were used in multiplicity comparison for determining non-inferiority

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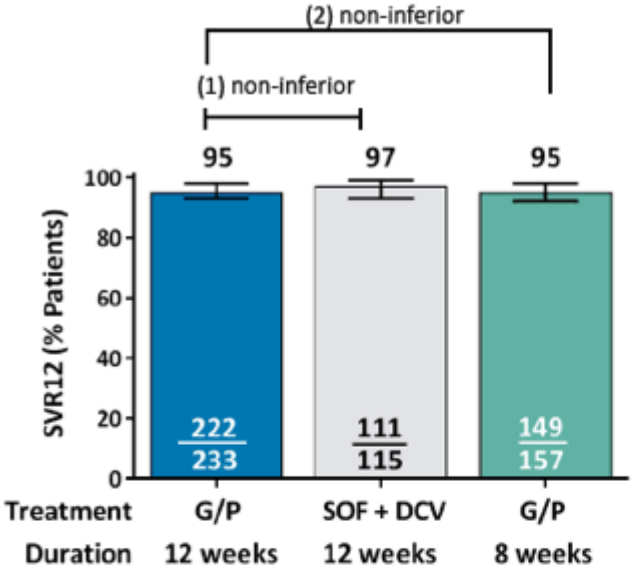

Non-inferiority:
Lower bound of the confidence interval (CI) of the difference in SVR12 must be above -6%*

(1) -1.2% (95% CI -5.6 – 3.1)

(2) -0.4% (97.5% CI -5.4 – 4.6)

Both G/P treatments met non-inferiority criteria for the primary endpoint

*Conventional statistical methods were used in multiplicity comparison for determining non-inferiority

All Treatment Outcomes

	2:1 randomized		Non-randomized
Outcome, n (%)	G/P 12 weeks N = 233	SOF + DCV 12 weeks N = 115	G/P 8 weeks N = 157
Sustained virologic response	222 (95)	111 (97)	149 (95)
Virologic Failure			
Breakthrough	1 (<1)	0	1 (1)
Relapse	3 (1)	1 (1)	5 (3)

All Treatment Outcomes

	2:1 randomized		Non-randomized
Outcome, n (%)	G/P 12 weeks N = 233	SOF + DCV 12 weeks N = 115	G/P 8 weeks N = 157
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Virologic Failure			
Breakthrough	1 (<1)	0	1 (1)
Relapse	3 (1)	1 (1)	5 (3)
Failure due to other reasons			
Discontinuation due to AE	1 (<1)	1 (1)	0
Withdrawal of consent	1 (<1)	0	0
Non-compliance	1 (<1)	0	0
Lost to follow-up / missing SVR12	4 (2)	2 (2)	2 (1)

AE, adverse event; G/P, coformulated glecaprevir/pibrentasvir; DCV, declatasvir; SOF, sofosbuvir; SVR12, sustained virologic response at post-treatment week 12

Resistance Analysis

SVR12 by baseline polymorphisms, n/N (%)	2:1 randomized G/P 12 weeks	2:1 randomized SOF + DCV* 12 weeks	Non-randomized G/P 8 weeks
NS3 only	26/26 (100)	–	14/15 (93)
NS5A only	35/36 (97)	20/21 (95)	34/36 (94)
NS3 + NS5A	6/7 (86)	–	5/7† (71)
None	151/153 (99)	89/89 (100)	94/95 (99)

Patients that prematurely discontinued treatment or were lost to follow-up were not included in the analysis
Polymorphisms detected by next-gen sequencing using 15% detection threshold at amino acid positions: NS3: 36, 56, 80, 155, 156, 166, 168; NS5A: 24, 28, 29, 30, 31, 32, 58, 92, 93
*NS3 sequences of samples were not determined
†One patient who had virologic failure had poor adherence and baseline polymorphisms in both NS3 and NS5A

Overall, 97% (mITT analysis; 371/381) of GT3 infected patients receiving G/P achieved SVR12

- 3% of patients (n = 10) had virologic failure
  - Common baseline polymorphisms: NS3 A166S‡ (n = 3); NS5A A30K‡ (n=5)
  - Common substitutions at failure: A30K+Y93H (n = 5); confers 69-fold resistance to PIB
- G/P for 8 weeks: 5/5 (100%) patients with Y93H at baseline achieved SVR12

‡Does not confer resistance to GLE or PIB

Patients that prematurely discontinued treatment or were lost to follow-up were not included in the analysis
Polymorphisms detected by next-gen sequencing using 15% detection threshold at amino acid positions: NS3: 36, 56, 80, 155, 156, 166, 168; NS5A: 24, 28, 29, 30, 31, 32, 58, 92, 93
*NS3 sequences of samples were not determined
†One patient who had virologic failure had poor adherence and baseline polymorphisms in both NS3 and NS5A

Summary of Adverse Events (AE)

Event, n (%)	2:1 randomized G/P 12 weeks N = 233	2:1 randomized SOF + DCV 12 weeks N = 115	Non-randomized G/P 8 weeks N = 157
Any AE	177 (76)	80 (70)	98 (62)
AE with possible relation to DAA	112 (48)	50 (43)	63 (40)
Serious AE	5 (2)	2 (2)	3 (2)
AE leading to study drug d/c	3 (1)	1 (1)	0
AEs occurring in ≥10% of patients			
Headache	60 (26)	23 (20)	31 (20)
Fatigue	44 (19)	16 (14)	20 (13)
Nausea	32 (14)	15 (13)	19 (12)

AE, adverse event; d/c, discontinuation; DAA, direct-acting antiviral; G/P, coformulated glecaprevir/pibrentasvir; DCV, daclatasvir; SOF, sofosbuvir

No serious AE was assessed as related to study drugs

Post-baseline Laboratory Abnormalities

Event, n (%)	2:1 randomized G/P 12 weeks N = 233	2:1 randomized SOF + DCV 12 weeks N = 115	Non-randomized G/P 8 weeks N = 157
Alanine aminotransferase*			
Grade ≥3 (>5 × ULN)	0	1 (1)†	0
Total bilirubin			
Grade ≥3 (>3 × ULN)	0	0	1 (1)‡
Hemoglobin			
Grade ≥2 (<10 g/dL)	0	0	0
Platelet Count			
Grade ≥2 (<75 × 10^9/L)	0	0	0
Neutrophil Count			
Grade ≥3 (<1.0 × 10^9/L)	1 (<1)§	0	0

d/c, discontinuation; G/P, coformulated glecaprevir/pibrentasvir; DCV, daclatasvir; SOF, sofosbuvir; ULN, upper limit of normal
*Increase in grade post nadir; †Increase did not result in treatment discontinuation and was not considered clinically relevant
‡Isolated increase in bilirubin (predominantly indirect fraction) 1 day after last dose of study drug; §Patient had isolated decrease 1 day post-treatment (normal all other visits)